

## The history of sexually transmitted diseases

# The history of non-gonococcal urethritis

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### The ancient world

Although the Bible has much to say about sexual behaviour, it contains few references to sexually transmitted diseases. Perhaps for this reason, a passage from Leviticus is often quoted. In the Authorised Version this reads: *When any man hath a running issue out of his flesh, because of this issue he is unclean.*<sup>1</sup> The word "issue" meant a discharge of matter from the body, and its management was described in detail. Men were advised to wash not only themselves, but objects with which they could have been in contact such as clothing, bedding and saddles. The "running issue" might have been a genital discharge. Traditionally it has been assumed that this was due to a gonococcal infection, but there is little collateral evidence that this existed in the ancient world.<sup>2</sup> Alternatively, the authors may have been referring to non-gonococcal urethritis (NGU). This idea is supported by the meaning of the word "issue" in the original Hebrew from which the Authorised Version was translated. A 12th century commentator, Rabbi Shlomo Yitzhaki, wrote that the Hebrew word "Zav" described a discharge the colour of "rice water" (Goldmeier D, personal communication). More recently Brim<sup>3</sup> favoured the words "as thin as watery dough, the colour of white of egg." These descriptions seem to be consistent with NGU rather than gonococcal urethritis.

The work of Greek and Roman medical writers did little to illuminate the problem of urethral discharge in the ancient world. Celsus (25 BC–50 AD) described *profusio seminis* as *the shedding of semen which occurs without sexual desire or erotic dreams, and in such a way that in time, the patient is consumed by wasting.*<sup>4</sup> Galen (130–200 AD) originated the word gonorrhoea (Greek gonos, semen, and rhoia, to flow). He defined it as "an unwanted secretion of semen without erection."<sup>5</sup> His contemporary Aretaeus wrote that *gonorrhoea is a persistent flow of semen without sensation, the fluid being thin, cold, colourless and unfruitful.*<sup>6</sup> Clearly, these ancients were not describing gonococcal urethritis as we know it today, with its pain, purulent discharge, strangury, chordee and so on. They may have been referring to spermatorrhoea,<sup>7</sup> the feelings of weakness and exhaustion being ascribed to the debilitating effects of loss of semen, "the principle of life." NGU is also a possibility and indeed some men today with persistent or recurrent disease complain of these symptoms.

### Gonorrhoea simplex

During the early Middle Ages an acute purulent urethritis was reported, first in Islam and later in Europe. Its false identification with

Galen's *gonorrhoea* came about because his writings were accepted as almost a medical Bible, so a name for the new disease had to be found in his works. *Gonorrhoea virulenta*—also known as clap, brenning and chaudepiss—was common, and there was no reference then to any less spectacular type of urethritis. When the epidemic of syphilis began in 1493 gonorrhoea and syphilis were assumed to arise from the same "virus". During the 16th century the violence of the initial outbreak of syphilis moderated, and *gonorrhoea virulenta* began to emerge not as a different disease but as a separate clinical entity. Subsequently, there were suggestions that urethritis might not always be caused by the "venereal virus". In a book published in 1737 Daniel Turner wrote that *gonorrhoea virulenta* was a *distemper where the matter of running is a sort of pus*, contrasting it with Galen's *gonorrhoea*, *the involuntary efflux of seed, where there is no venereal taint.*<sup>8</sup> John Astruc (1754) commented: *Besides the virulent Gonorrhoea which we have already described there is another venereal disorder of the urethra . . . in which the patient is afflicted with a sharp burning dysuria without any discharge of purulent semen or seminal humour. This is sometimes called a dry gonorrhoea, but this name is very improper, as it is a contradiction in terms.*<sup>9</sup> Thirty years later John Hunter observed that the urethra was subject to inflammation from various causes besides the "venereal poison". *Such may be called gonorrhoea simplex . . . having nothing of the venereal taint in them, although those persons who have formerly been subject to virulent gonorrhoea are most liable to them.*<sup>10</sup>

Benjamin Bell, who unlike Hunter believed that syphilis and gonorrhoea were separate diseases, held a similar view of *gonorrhoea simplex*. He wrote that this was a puriform [purulent] discharge which could be caused by anything which excited urethral inflammation for example, repeated intercourse with a woman with leucorrhoea, horseback riding and being *overheated with wine.*<sup>11</sup> It is clear that neither Hunter nor Bell regarded *gonorrhoea simplex* primarily as a sexually transmitted disease, although it could be associated with coitus. It appears that the term covered several conditions. Bell stated that it could be followed by swelling of the testicles, and sometimes *a flow of matter from the urethra has alternated with pains in the knees and other large joints.* To the modern reader these remarks imply that at least some of Bell's patients with *gonorrhoea simplex* had NGU with secondary epididymitis or reactive arthritis.

### Blennorrhagia

In the early part of the 19th century the con-

sensus was that urethritis was due to either a venereal infection—gonorrhoea—or to a non-specific inflammation which, although it might follow sexual intercourse, was not strictly “venereal” because it could follow other events. The possibility that a non-specific irritant could cause a urethral discharge was confirmed by Swediaur in 1805.<sup>12</sup> He instilled an aqueous solution of ammonia into his urethra, provoking a violent urethritis. He introduced the word *blennorrhagia*, which meant any inflammation of genital mucosae. This term was unfortunate and led to much confusion. It was adopted by Ricord, at the time the doyen of French venereologists. According to him, urethral blennorrhagia was caused by the action of various ill-defined irritants (phlogogens). These included *fluor albus* and in general any *morbid secretion* which might come into contact with the urethra. So far, this was a restatement of what had been said before, but Ricord went further. Having said that the urethral discharge might be mucoid, mucopurulent or purulent he stated that even *virulent urethral blennorrhoea* did not have a single specific cause,<sup>13</sup> thus doing away with the earlier distinction between *gonorrhoea virulenta* and *gonorrhoea simplex*. The theory of non-specific phlogogens was widely accepted by Ricord’s contemporaries. It was actively promulgated by his disciple William Acton,<sup>14</sup> and supported by many venereologists, including Fournier in France and Bumstead in the USA. But others disagreed. Rollet of Lyons, for example, insisted that *gonorrhoea virulenta* was due to a specific “virus”, and that every individual person with the disease had contracted the virus from somebody else.<sup>15</sup> The only way in which this dispute could be settled was through bacteriological research. This had been progressing rapidly since the studies of Pasteur and Koch, and in 1879 Albert Neisser, working in Breslau, discovered the gonococcus, an event which made possible the scientific study of urethritis.

#### NGU after Neisser 1880–1970

##### *Aetiology*

For the first few years after 1879 it was believed that all cases of acute urethritis were gonococcal, failure to identify the organisms in stained urethral smears being attributed to faulty technique.<sup>16</sup> But the invention of Gram staining and the development of culture systems during the 1880s made the laboratory diagnosis of gonorrhoea more accurate; false positive results were reduced, and papers on NGU (*urethritis non-gonorrhoeica*) began to appear. Nevertheless, some physicians still refused to accept that this “new” disease existed. Bacteriology was developing rapidly in those days, and the possibility of a bacterial cause for NGU was soon considered. Some urethral discharges indeed showed the presence of non-gonococcal organisms. Among these were staphylococci, streptococci, Gram-positive diplococci, diphtheroids and coliforms,<sup>17 18</sup> which were recovered not only from men with NGU, but from their sex partners as

well. Although many workers postulated the existence of an acute bacterial urethritis, the resemblance of many suspect organisms to those present in the normal flora led to scepticism, and Barlow for one contended that before a causal role could be accepted, any organisms recovered from men with NGU should be examined for pathogenicity by human experiment.<sup>19</sup>

In the pre-antimicrobial era residual urethritis after an attack of gonorrhoea was common. By convention, an attack which lasted for more than six weeks had become “chronic”. However, after the discovery of *N gonorrhoeae* it was realised that in many cases of “chronic gonorrhoea” the organisms were no longer demonstrable. It was suggested that gonococci were lurking in the deeper tissues and could be reactivated later, but some workers did not agree with this. The American physician Robert Taylor wrote: *Many men with anterior and posterior urethritis have intercourse over long periods without communicating gonorrhoea to their partners. In these cases the gonococcus has disappeared. The phoenix-like character given by many is, in most cases a myth.*<sup>20</sup> In 1911 von Wahl roundly declared that there was no such thing as chronic gonorrhoea; in these cases the persistent discharge was due to NGU caused by a mixed infection in the first place.<sup>21</sup> In modern terminology, they had postgonococcal urethritis.

Another line of enquiry began with the description of an “aseptic urethritis” in which conventional microscopy and culture revealed no micro-organisms. In 1901, Waelsch described a group of patients whose disease was characterised by a relatively long incubation period, mild symptoms and signs and a prolonged intractable course.<sup>22</sup> Other clinicians published details of similar cases, and in 1914 Glingar recorded their urethroscopic appearances: an erythematous mucous membrane, with multiple soft infiltrates “standing up from the surface”.<sup>23</sup> Further reports of this “millet seed” or “sago grain” urethritis made it clear that if this had an infective basis, the agent responsible was not known. The problem was unexpectedly clarified when Halberstaedter and Von Prowazek found cytoplasmic inclusions in cells from the eyes of monkeys experimentally infected with trachoma.<sup>24</sup> Soon after this they found apparently identical inclusions in conjunctival cells from some infants with non-gonococcal ophthalmia neonatorum, and Heymann discovered them in the cervix of the mother, and the urethra of the father of one of these babies.<sup>25</sup> There was immediate speculation that an inclusion-forming organism, tentatively called chlamydozoon, might be the cause of at least some cases of aseptic urethritis, and Lindner soon found inclusions in the urethral cells of four out of ten men with NGU; he suggested the possible existence of a “genital trachoma”.<sup>26</sup> Other workers noted the similarity between the urethral follicles in some men with “Waelsch urethritis” and those seen in trachoma. Sadly, these pioneering studies were not pursued and were largely forgotten until, fifty years later,

the importance of chlamydiae in the pathogenesis of NGU and its complications was finally realised.

In 1913 the French physician Georges Luys summarised current opinion on the causes of NGU: (1) Infection by "common organisms", which could usually be recovered from the female partner—"primary venereal urethritis"; (2) Aseptic inflammations due to excessive sex or alcohol, or intercourse during menstruation; (3) Chemical or physical irritants.<sup>27</sup> This classification, derived partly from early bacteriological studies and partly from Ricord's theory of non-specific phlogogens, was repeated by successive authors for many years. But such interest in NGU as there had been was declining. In 1920 McDonagh described it as *rare and poorly understood*.<sup>28</sup> In successive editions of his book on venereal diseases (1919–1931) Harrison referred to it, but only in passing.<sup>29</sup> The *British Journal of Venereal Diseases* was founded in 1926, but contained nothing about NGU until 1933. An exception to the prevailing ennui concerned the role of *Trichomonas vaginalis*. In 1894 Miura had identified it in a freshly voided urine sample from a man, and suggested that it might be sexually transmissible.<sup>30</sup> During the 1920s cases of NGU associated with the presence of trichomonads were reported.<sup>31</sup> Some of the patients had a persistent urethral discharge after an attack of gonorrhoea, and others gave a short history of dysuria and discharge after unprotected intercourse; in most cases the female partners were also infected. On the strength of this, the organism was added to the causes of NGU.

There were no further developments, or indeed interest, in the aetiology of NGU during the 1930s and 1940s. During the war years many venereologists, like their predecessors 60 years before, maintained that there was no such thing as NGU, and that the gonococcus was always lurking in the background. Some said that many cases of "so-called NGU" could be explained by the surreptitious use of a sulphonamide for the treatment of gonorrhoea,<sup>32</sup> but others pointed out that such cases proved the existence of primary mixed infections leading to postgonococcal urethritis, as von Wahl had maintained in 1911. After the Second World War it became obvious not only that NGU was now common, but that very little was known about it. The time was ripe for a complete reappraisal of the subject, and this was begun by Harkness, who in 1950 published a comprehensive monograph on all aspects of the condition.<sup>33</sup> He listed over 70 causes; many of them were familiar from the early literature, but he included two newcomers, chlamydial and mycoplasmal infection. Harkness had studied the work of the early masters, Halberstaedter, von Prowazek, Heymann and Lindner. He revived the concept of "Waelsch urethritis" and its trachoma-like urethrosopic features, and he identified inclusions in urethral smears from some men with NGU. Like his predecessors, he was severely handicapped by the lack of sensitive and specific diagnostic methods, and for this reason did not regard chlamydial infection as

common. Nevertheless, his work was influential—particularly in the UK—in reawaking interest in these subjects at a time when they were considered to be of little importance.

The prevalence of "inclusion urethritis" was believed to be small, accounting for less than 5% of cases of NGU. There had been several attempts to cultivate the agent *in vitro*, but it was not until the late 1950s that it was isolated by incubation of the yolk sacs of embryonated hens' eggs.<sup>34</sup> In 1966 Dunlop *et al* applied this technique to study men with NGU, and two of nine men yielded isolates.<sup>35</sup> At this time the organisms now classified as *C. trachomatis* were often called "TRIC agents" (TRachoma, Inclusion Conjunctivitis). The yolk sac method was cumbersome, and not suitable for large scale surveys, and in this and other respects the cell culture technique developed by Gordon and Quan<sup>36</sup> was a notable advance. In a large series of studies it was now shown that chlamydia could be isolated from 30 to 40% of men with NGU; the isolation rate from sexually active men without NGU was below five percent. These results, together with subsequent serological and treatment studies, established a major role for chlamydia in the pathogenesis of NGU and its complications.<sup>37</sup>

The mycoplasmas were later additions to the supposed causes of NGU, and their study gave a great deal of trouble. The first isolation of a mycoplasma from a human was in 1937, when Dienes and Edsall recovered organisms from an abscess of a Bartholin's gland.<sup>38</sup> Because they resembled microbes known to cause a respiratory disease in cattle, they were first called pleuropneumonia-like organisms (PPLO); they were probably *Mycoplasma hominis*. In 1942 there were reports of the recovery of PPLO from urethral and prostatic secretions,<sup>39, 40</sup> which led to a series of attempts to decide whether they were a cause of NGU. The early studies seemed to support this idea, because while at least 50% of men with NGU were infected, the isolation rate in healthy men was very low. But later work showed that when the control groups were more closely matched to the groups with NGU, particularly in sexual experience, this difference disappeared. By the early 1960s it had been concluded that *M. hominis* was not a significant cause of NGU.<sup>41</sup>

The role of *Ureaplasma urealyticum* received stronger support. In 1954 Shepard,<sup>42</sup> culturing urethral scrapings from men with NGU, found colonies whose diameter was only 10% of those of *M. hominis*; he called them "T-form" (T for tiny). Once again it was thought that a possible cause of NGU had been found, and another series of isolation studies followed. About half of these showed that T-form mycoplasmas were isolated more often from men with NGU than from control groups without disease, but later work showed that most of these differences were due to the use of poorly matched controls.<sup>43</sup> The unwelcome conclusion was that this laborious work had failed to establish the pathogenicity of T-mycoplasmas in the male urethra. In the early

1970s another series of investigations began, involving quantitative cultures, differential antimicrobial therapy, animal experiments and conjoined studies of T-mycoplasmas and *C trachomatis*. From these it was concluded that these mycoplasmas were responsible for some cases of NGU, although the proportion was unclear.<sup>44</sup> In 1974 they were assigned to a separate genus, and given the name *Ureaplasma urealyticum*. For many years this organism was the last cause of NGU to be positively identified. From time to time other microbes were suggested—for example *Corynebacterium vaginale*, coagulase-negative staphylococci, so-called NGU corynebacteria and *Haemophilus equigenitalis*—but the proposals came to nothing. Recently, however, there has been some compelling evidence that *M genitalium* is one of the causes of NGU, and this organism is now being intensively studied.<sup>45</sup>

### Diagnosis and treatment

In the 18th century the diagnosis of urethritis was based simply on the presence of a urethral discharge. An approximate distinction between *gonorrhoea virulenta* and *gonorrhoea simplex* depended on the circumstances of the case, the length of the incubation period and the intensity of the urethral inflammation. Men with mild urethritis were often left untreated, or were prescribed bland fluids and simple oral medication; bleeding, vesication and urethral lavage were reserved for those with a severe infection, particularly *gonorrhoea virulenta*. Ricord approached the differential diagnosis of urethritis by putting emphasis on *the quantity and quality of the pus*. Some surgeons, he wrote, *lay great stress on the smell of the secretions, and they can, by means of this character, distinguish a virulent from a simple blennorrhagia*.<sup>46</sup> Ricord was indirectly responsible for the development of the two-glass urine test when he observed that *the posterior urethra drains into the bladder, but the anterior into the shirt*. The test itself was devised by a London surgeon, Henry Thompson, in 1868. It was originally intended to distinguish between a urinary tract infection and gonorrhoea or gleet: *Let the man pass two or three tablespoons [of urine] first so as to sweep out whatever may be there, which may be put into a separate bottle, after which you will get a pure specimen—the renal secretion plus anything in the bladder*.<sup>47</sup> Thompson's test underwent various modifications and was eventually used to differentiate anterior from posterior urethritis. The early masters distinguished the two clinically, and treated them differently. When urethral irrigation for the treatment of urethritis was introduced by Janet in 1880 the distinction was maintained. If the second urine specimen was clear, only the anterior urethra was irrigated; otherwise, the whole urethra as far as the bladder neck was treated. During the first half of the 20th century, the diagnosis of NGU depended primarily on the microscopy of a stained urethral smear, whose main purpose was to establish or exclude gonorrhoea, but also to demonstrate the presence of polymorphonuclear leucocytes. Sometimes the test

was repeated, but urethral culture for *N gonorrhoeae* was very unusual. A two-glass urine test and serological tests for syphilis completed the laboratory investigations.

A mild attack of NGU was treated with alkalies, or urinary antiseptics such as sandalwood oil, mandelic acid or hexamine. For a more severe attack, particularly with evidence of posterior urethritis, urethrovesical irrigations with potassium permanganate or mercury oxycyanide were used. Tests of cure included a further two-glass test, examination of the prostatic fluid for leucocytosis, the passage of a urethral sound and sometimes urethroscopy. The sulphonamides were first used for the treatment of gonorrhoea in the late 1930s, and the early results were so encouraging that they were soon tried for the treatment of NGU—empirically, because its cause was unknown. The results were variable, and at best the cure rate barely exceeded 50%. A further disappointment was that both penicillin and streptomycin were found to be completely ineffective. During the 1940s some clinicians treated NGU with sulphonamides despite their indifferent results, but others persisted in urethrovesical irrigation. In 1953 combination therapy with a single injection of streptomycin followed by a short course of a sulphonamide, was proposed as a catch-all treatment for urethritis, gonococcal or non-gonococcal.<sup>48</sup> Good results were claimed in the treatment of NGU, and for some years the regimen became quite popular, although it was never subjected to a strict clinical trial. The first tetracycline, chlortetracycline, appeared in 1948, and clinical trials for NGU began three years later. The antibiotic gave results far better than anything which had been tried before, although some clinicians preferred the streptomycin-sulphonamide combination on the grounds of cost and its inactivity against incubating syphilis. By the mid 1950s, however, tetracyclines were being recommended for the routine treatment of NGU.<sup>49</sup> A scientific rationale for this treatment was found later, that tetracyclines were active *in vitro* against both *C trachomatis* and *U urealyticum*. Urethrovesical irrigations were gradually abandoned, and systemic therapy made the old distinctions between anterior and posterior urethritis less important. Some of the strict tests of cure—for example, insistence on urethral instrumentation in all cases—were gradually relaxed.

If the criteria for the cure of NGU became more relaxed, those for diagnosis became more stringent. The number of leucocytes on a urethral smear had been specified only in general terms, such as "multiple", "abundant" and so on, and the first-catch urine usually received only a naked eye inspection, although sometimes urinary "threads" were examined by microscopy as a wet preparation to confirm leucocytosis. Evidently only clinically obvious cases of NGU were being diagnosed; indeed, in 1955 Gartman and Leibovitz, who studied more than 500 men with this diagnosis, wrote that "gross pyuria is invariable".<sup>49</sup> As time went by the impression grew among clinicians that NGU was being underdiagnosed, and

during the 1960s it was realised that some infections became apparent only after the patient had not passed urine for several hours, or overnight.<sup>50</sup> The "early morning smear" became a familiar feature of practice in many British clinics. More stringent requirements in terms of the number of leucocytes per high power field on microscopy, and the examination of centrifuged first-catch urine specimens, belong to the modern era.

### Public health aspects

Few countries produced data on the incidence of NGU. The number of new cases in England and Wales were first returned from treatment centres in 1951, when 10 794 cases were reported; this figure increased steadily for many years. The term "non-specific urethritis" came into use at this time, particularly in the UK, but it was (and remains) inappropriate because in many cases a specific cause could be shown. The bulk of NGU had been regarded as a venereal infection, but in 1958 Boyd *et al* pointed out that in some men there had been no recent change of sex partner.<sup>51</sup> This was in accord with early opinion. Bell<sup>10</sup> had written that *gonorrhoea simplex* was not invariably sexually transmitted. Nevertheless, in most cases the history strongly supported that NGU had been contracted from a female partner. Unfortunately, there was no apparent clinical counterpart in women, and for several years a misleading diagnosis of "non-specific genital infection" came into use in the UK. This was partly the expression of an epidemiological belief, but also included a miscellany of conditions—for example, abacterial pyuria, cervicitis and Bartholinitis—which had little connection with each other. Since it was so difficult to decide which partners of men with NGU were infected and which were not there was clearly a case for treating all contacts epidemiologically, and this was gradually accepted despite vociferous objections from physicians were opposed to "treatment before diagnosis."

There can be no doubt that for many years NGU was not taken seriously. It was regarded as a condition which caused minor inconvenience of no great significance. Contact tracing and epidemiological treatment were desultory, although the escalation of the epidemic as shown by the official statistics was there for all to see. A major change in emphasis came from research on *C trachomatis*, from which it emerged that this organism was not only the major cause of NGU but was responsible for all its serious complications. It had been known since the 18th century that *gonorrhoea simplex* could lead to epididymitis, and in 1977 the role of *C trachomatis* in this disease was shown.<sup>52</sup> Even more important was the connection between chlamydial infection and salpingitis, which was first established by Mardh and his colleagues in 1977.<sup>53</sup> The connection between chlamydia, NGU and ophthalmia neonatorum had been recorded by Heymann in 1910,<sup>24</sup> and modern technology allowed this role to be explored in depth and

new syndromes such as neonatal afebrile pneumonia to be identified.

It has taken a long time to convince the medical and scientific community that NGU is an important disease both in itself and as a pointer to far-reaching consequences. It is obvious that there are many unsolved problems—the aetiology of at least 20% of new cases, the reasons for recurrences and the diagnosis of infected sex contacts are some—requiring serious investigation. Will this be forthcoming? The history of NGU is hardly one of unalloyed triumph, and many mistakes and omissions have occurred. It is to be hoped that in the current concern about other infections the importance of this ancient disease will not be forgotten.

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